

ENT COOPERATION TREA

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION
(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
 United States Patent and Trademark
 Office
 Box PCT
 Washington, D.C.20231
 ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 11 July 2000 (11.07.00)	Assistant Commissioner for Patents United States Patent and Trademark Office Box PCT Washington, D.C.20231 ETATS-UNIS D'AMERIQUE
International application No. PCT/EP99/07689	Applicant's or agent's file reference 0098436-mpgs
International filing date (day/month/year) 13 October 1999 (13.10.99)	Priority date (day/month/year) 30 October 1998 (30.10.98)
Applicant BUCHHOLZ, Herwig et al	

1. The designated Office is hereby notified of its election made:

in the demand filed with the International Preliminary Examining Authority on:

11 April 2000 (11.04.00)

in a notice effecting later election filed with the International Bureau on:

2. The election was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Maria Kirchner Telephone No.: (41-22) 338.83.38
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K 31/00		A2	(11) International Publication Number: WO 00/25764 (43) International Publication Date: 11 May 2000 (11.05.00)
<p>(21) International Application Number: PCT/EP99/07689</p> <p>(22) International Filing Date: 13 October 1999 (13.10.99)</p> <p>(30) Priority Data: 60/106,205 30 October 1998 (30.10.98) US</p> <p>(71) Applicant (<i>for all designated States except US</i>): MERCK PATENT GMBH [DE/DE]; Frankfurter Strasse 250, D-64293 Darmstadt (DE).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (<i>for US only</i>): BUCHHOLZ, Herwig [DE/DE]; Auf dem Mühlberg 75, D-60599 Frankfurt (DE). MEDUSKI, Jerzy, D. [US/US]; 6806 Vista Delmar Lane, Playa Del Rey, CA 90293-7640 (US).</p> <p>(74) Common Representative: MERCK PATENT GMBH; Frankfurter Strasse 250, D-64293 Darmstadt (DE).</p>		<p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>Without international search report and to be republished upon receipt of that report.</i></p>	
<p>(54) Title: COMPOSITIONS FOR THE TREATMENT AND PREVENTION OF CARDIOVASCULAR DISEASES</p> <p>(57) Abstract</p> <p>Compositions comprising one or more active ingredients and, optionally, one or more nutritional substances, solid, liquid and/or semiliquid excipients or auxiliaires, wherein the active ingredients consist of a) a <u>component A</u> consisting of one or more compounds selected from methyl and methylene donors, b) a <u>component B</u> consisting of one or more methyl transporters, and c) a <u>component C</u> consisting of one or more bioflavonoids are well-suited for the treatment and prevention of transmethylation disorders, preferably cardiovascular diseases such as atherogenic and thrombogenic diseases.</p>			

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Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
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AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
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PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K 31/205, 31/505, 31/195, 31/35, A23L 1/305, A23L 1/30, 1/302	A3	(11) International Publication Number: WO 00/25764 (43) International Publication Date: 11 May 2000 (11.05.00)
(21) International Application Number: PCT/EP99/07689		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
(22) International Filing Date: 13 October 1999 (13.10.99)		
(30) Priority Data: 60/106,205 30 October 1998 (30.10.98) US		
(71) Applicant (for all designated States except US): MERCK PATENT GMBH [DE/DE]; Frankfurter Strasse 250, D-64293 Darmstadt (DE).		
(72) Inventors; and		
(75) Inventors/Applicants (for US only): BUCHHOLZ, Herwig [DE/DE]; Auf dem Mühlberg 75, D-60599 Frankfurt (DE). MEDUSKI, Jerzy, D. [US/US]; 6806 Vista Delmar Lane, Playa Del Rey, CA 90293-7640 (US).		Published <i>With international search report.</i>
(74) Common Representative: MERCK PATENT GMBH; Frankfurter Strasse 250, D-64293 Darmstadt (DE).		(88) Date of publication of the international search report: 13 July 2000 (13.07.00)

(54) Title: COMPOSITIONS FOR THE TREATMENT AND PREVENTION OF CARDIOVASCULAR DISEASES

(57) Abstract

Compositions comprising one or more active ingredients and, optionally, one or more nutritional substances, solid, liquid and/or semiliquid excipients or auxiliaires, wherein the active ingredients consist of a) a component A consisting of one or more compounds selected from methyl and methylene donors, b) a component B consisting of one or more methyl transporters, and c) a component C consisting of one or more bioflavonoids are well-suited for the treatment and prevention of transmethylation disorders, preferably cardiovascular diseases such as atherogenic and thrombogenic diseases.

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INTERNATIONAL SEARCH REPORT

Int'l Application No

PCT/EP 99/07689

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/205 A61K31/505 A61K31/195 A61K31/35 A23L1/305
 A23L1/30 A23L1/302

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A23L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 347 864 A (STRYDOM ANDRIES JOHANNES CORNE) 27 December 1989 (1989-12-27) abstract; claims 1,3,6,7	1-12
X,P	WO 98 50051 A (LOCKETT CURTIS) 12 November 1998 (1998-11-12) abstract page 5; claim 1; example 1	1-12
X	WO 98 33494 A (KOSBAB JOHN V) 6 August 1998 (1998-08-06) abstract page 36, line 26-33 page 13, line 20; claim 30; table 3	1-12
X	FR 2 583 640 A (BERDAL PASCAL) 26 December 1986 (1986-12-26) claims 3-5	1-12
		-/-

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the International filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

18 April 2000

Date of mailing of the international search report

26/04/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Gonzalez Ramon, N

INTERNATIONAL SEARCH REPORT

Int'l Application No
PCT/EP 99/07689

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 98 18491 A (BURGSTINER JACQUELINE COOK & L) 7 May 1998 (1998-05-07) page 22 -page 23; claim 10; example 1	1-12
Y	DUELL P B ET AL: "HOMOCYST(E)INE: AN IMPORTANT RISK FACTOR FOR ATHEROSCLEROTIC VASCULAR DISEASE" CURRENT OPINION IN LIPIDOLOGY, GB, LONDON, vol. 8, no. 1, February 1997 (1997-02), pages 28-34, XP000853544 ISSN: 0957-9672 page 32, column 1; table 2	1-12
E	US 5 976 568 A (RILEY PATRICIA A) 2 November 1999 (1999-11-02) abstract; claims 1,5; tables 2,3	1-12

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 99/07689

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.: **1-12** because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of Invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-12

Present claims 1-12 relate to compounds defined by reference to a desirable characteristic or property, namely "methyl and methylene donors", "methyl transporters". The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds.

Moreover, the expression "bioflavonoids" comprises numerous possible compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Also the description of the therapeutic application as "transmethylation disorders" is not clear. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds specifically mentioned in the examples and the claims and the therapeutic applications specified in claim 11 with due regard to the general idea underlying the present application.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internatinal Application No

PCT/EP 99/07689

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP 0347864	A 27-12-1989	AU	2999192 A	04-02-1993
		AU	3673789 A	04-01-1990
		DK	313989 A	25-12-1989
		JP	2067216 A	07-03-1990
		MC	2041 A	30-05-1990
		NO	892617 A	27-12-1989
		NZ	229670 A	28-07-1992
		ZA	8904797 A	28-03-1990
WO 9850051	A 12-11-1998	AU	2993297 A	27-11-1998
WO 9833494	A 06-08-1998	AU	6141498 A	25-08-1998
FR 2583640	A 26-12-1986	NONE		
WO 9818491	A 07-05-1998	NONE		
US 5976568	A 02-11-1999	NONE		

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 0098436-mpgs	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/EP 99/ 07689	International filing date (day/month/year) 13/10/1999	(Earliest) Priority Date (day/month/year) 30/10/1998
Applicant MERCK PATENT GMBH et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :
 - contained in the international application in written form.
 - filed together with the international application in computer readable form.
 - furnished subsequently to this Authority in written form.
 - furnished subsequently to this Authority in computer readable form.
 - the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
 - the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. **Certain claims were found unsearchable** (See Box I).

3. **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

- the text is approved as submitted by the applicant.
- the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

- the text is approved as submitted by the applicant.
- the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

- as suggested by the applicant.
- because the applicant failed to suggest a figure.
- because this figure better characterizes the invention.

None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 99/07689

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.: 1-12 because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-12

Present claims 1-12 relate to compounds defined by reference to a desirable characteristic or property, namely "methyl and methylene donors", "methyl transporters". The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. Moreover, the expression "bioflavonoids" comprises numerous possible compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Also the description of the therapeutic application as "transmethylation disorders" is not clear. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds specifically mentioned in the examples and the claims and the therapeutic applications specified in claim 11 with due regard to the general idea underlying the present application.

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 99/07689

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/205 A61K31/505 A61K31/195 A61K31/35 A23L1/305
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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A23L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	FR 2 583 640 A (BERDAL PASCAL) 26 December 1986 (1986-12-26) claims 3-5 ---	1-12
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- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

18 April 2000

Date of mailing of the international search report

26/04/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
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 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Gonzalez Ramon, N

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 99/07689

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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E	US 5 976 568 A (RILEY PATRICIA A) 2 November 1999 (1999-11-02) abstract; claims 1,5; tables 2,3 -----	1-12

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			DK	313989 A	25-12-1989
			JP	2067216 A	07-03-1990
			MC	2041 A	30-05-1990
			NO	892617 A	27-12-1989
			NZ	229670 A	28-07-1992
			ZA	8904797 A	28-03-1990

WO 9850051	A	12-11-1998	AU	2993297 A	27-11-1998

WO 9833494	A	06-08-1998	AU	6141498 A	25-08-1998

FR 2583640	A	26-12-1986	NONE		

WO 9818491	A	07-05-1998	NONE		

US 5976568	A	02-11-1999	NONE		

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International application No. PCT/EP99/07689

Comments on item V

1. Composition comprising components A, B and C, as defined in claims 1-2 and 5-11 are known from the following documents:

D1: EP-A-0 347 864; 27 December 1989 (see page 3, lines 7-13);

D2: WO 98 33494 A; 6 August 1998 (see Table 3);

D3: FR-A-2 583 640; 26 December 1986 (see claims 1, 3, 5); and

D4: WO 98 18491 A; 7 May 1998 (see p.21, l.10 - p.23, l.11).

The subject-matter of claim 1 is construed as a composition containing A, B and C, wherein many other ingredients may be present, due to the use of the term "comprising", which leaves the number of components open. For this reason, the compositions described in D1-D4 take away the novelty of claim 1, even though they contain other components in addition to A, B and C.

- 1.1 It should be noted that a claim with the wording "Composition consisting of A, B and C" would not be regarded as inventive unless a surprising effect was proven with respect to the known compositions disclosed in D1-D4.
- 1.2 Claims 7-11 lack novelty for the reasons set forth in section 1, as they refer to the same compositions of claims 1-6. It appears that the compositions described in D1-D4 would also be suitable for the treatment and prevention of the disorders mentioned in claims 7-11 (see PCT Guidelines, III, 4.8). In any case, the specific therapeutic uses indicated in the aforementioned claims have been already disclosed: see D1, p.1, l.1-9 and D2, p.3, l.10-12.
- 1.3 The subject-matter of claim 12 seems to lack novelty for the following reasons: even though the term "transmetilation disorders" is unclear (see Item VIII), cardiovascular diseases appear to be included therein, and D1 and D2 disclose the use of a composition containing A, B and C for the preparation of a composition for treating cardiovascular disorders (see at the places indicated in section 1.2).
2. Having regard to the present prior art the subject-matter of claims 3-4 seems to be novel, since all the four documents cited refer to folic acid. However, it could not

**INTERNATIONAL PRELIMINARY
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International application No. PCT/EP99/07689

be regarded as inventive, since it is generally known to the skilled in the art that folic acid is naturally metabolized to THFA, and THFA becomes 5-methyl THFA during the folate cycle. There seems to be no technical difference in using either folic acid or one of its metabolites, especially as D5 (DUELL ET AL; CURRENT OPINION IN LIPIDOLOGY, vol. 8, no. 1, February 1997, pages 28-34) states that the levels of homocysteine, which is an important risk factor for atherosclerotic vascular disease, can be reduced with pharmacological doses of folic acid (see the abstract and Figures 2-3).

Comments on item VI

1. Certain published documents (Rule 70.10)

Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
PCT/US97/07122	12.11.98	05.05.97	
US-A-5 976 568	02.11.99	21.02.97	

Comments on item VII

1. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1-D4 is not mentioned in the description, nor are these documents identified therein.
2. Those parts of the description referring to the spirit of the invention (see p.12) should be deleted (see PCT Guidelines, III, 4.3a).

Comments on item VIII

1. Claim 1 does not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. Components A and B are defined

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/07689

I. Basis of the report

1. This report has been drawn on the basis of (substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).):
Description, pages:

1-13 as originally filed

Claims, No.:

1-12 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- the language of publication of the international application (under Rule 48.3(b)).
- the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- contained in the international application in written form.
- filed together with the international application in computer readable form.
- furnished subsequently to this Authority in written form.
- furnished subsequently to this Authority in computer readable form.
- The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- the description, pages:
- the claims, Nos.:
- the drawings, sheets:

5. This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

PATENT COOPERATION TREATY

PCT

REC'D 29 DEC 2000

WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 0098436-mpgs	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP99/07689	International filing date (day/month/year) 13/10/1999	Priority date (day/month/year) 30/10/1998

International Patent Classification (IPC) or national classification and IPC
A61K31/205

Applicant

MERCK PATENT GMBH et al.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I Basis of the report
- II Priority
- III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV Lack of unity of invention
- V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI Certain documents cited
- VII Certain defects in the international application
- VIII Certain observations on the international application

Date of submission of the demand 11/04/2000	Date of completion of this report 27.12.2000
Name and mailing address of the International preliminary examining authority European Patent Office	Authorized officer



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(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims 3, 4
	No: Claims 1, 2, 5-12
Inventive step (IS)	Yes: Claims
	No: Claims 1-12
Industrial applicability (IA)	Yes: Claims 1-12
	No: Claims

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

**INTERNATIONAL PRELIMINARY
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International application No. PCT/EP99/07689

be regarded as inventive, since it is generally known to the skilled in the art that folic acid is naturally metabolized to THFA, and THFA becomes 5-methyl THFA during the folate cycle. There seems to be no technical difference in using either folic acid or one of its metabolites, especially as D5 (DUELL ET AL; CURRENT OPINION IN LIPIDOLOGY, vol. 8, no. 1, February 1997, pages 28-34) states that the levels of homocysteine, which is an important risk factor for atherosclerotic vascular disease, can be reduced with pharmacological doses of folic acid (see the abstract and Figures 2-3).

Comments on item VI

1. Certain published documents (Rule 70.10)

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PCT/US97/07122	12.11.98	05.05.97	
US-A-5 976 568	02.11.99	21.02.97	

Comments on item VII

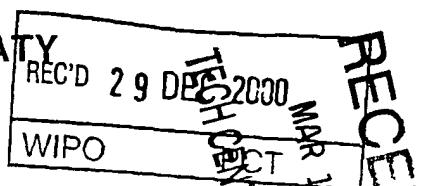
1. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1-D4 is not mentioned in the description, nor are these documents identified therein.
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Comments on item VIII

1. Claim 1 does not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. Components A and B are defined

PATENT COOPERATION TREATY

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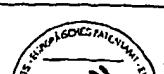
INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

04870

Applicant's or agent's file reference 0098436-mpgs	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP99/07689	International filing date (day/month/year) 13/10/1999	Priority date (day/month/year) 30/10/1998
International Patent Classification (IPC) or national classification and IPC A61K31/205		
<p>Applicant MERCK PATENT GMBH et al.</p> <p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 6 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of sheets.</p> <p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> I <input checked="" type="checkbox"/> Basis of the report II <input type="checkbox"/> Priority III <input type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input checked="" type="checkbox"/> Certain documents cited VII <input checked="" type="checkbox"/> Certain defects in the international application VIII <input checked="" type="checkbox"/> Certain observations on the international application 		

Date of submission of the demand 11/04/2000	Date of completion of this report 27.12.2000
Name and mailing address of the international preliminary examining authority European Patent Office	Authorized officer



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**INTERNATIONAL PRELIMINARY
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by a result to be achieved, which merely amounts to a statement of the underlying problem. The technical features (type of compounds, reaction conditions...) necessary for achieving this result should be added.

2. The term "transmetilation disorders", in claims 7 and 12, renders these claims unclear, since it does not have a generally accepted meaning.

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International application No. PCT/EP99/07689

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